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| 10/541,894 | 12/02/2005 | Karin Klokke | 930008-2202 (BOE0003US.NP) | 6226 |
| 7590 Jane Massey Licata, Esquire Licata & Tyrrell P.C. 66 E. Main Street Marlton, NJ 08053 | | | EXAMINER SASAN, ARADHANA | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|--|--|
| Office Action Summary | Application No. 10/541,894 | Applicant(s) KLOKKERS ET AL. | |
| | Examiner ARADHANA SASAN | Art Unit 1615 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 December 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24-33 and 35-48 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24-33 and 35-48 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 10/31/08 are acknowledged.
2. Claims 1-2 and 34 were cancelled. Claims 24, 41, and 46 were amended.
3. Claims 24-33 and 35-48 are included in the prosecution.

Continued Examination under 37 CFR 1.114

4. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/31/08 has been entered.

Response to Arguments

Rejection of claims 24-31, 34-35, 38, 40-43 and 45-48 under 35 USC § 102(b)

5. In light of Applicants' cancellation of claim 34, the rejection with respect to this claim is rendered moot.
6. Applicants' arguments, see Page 8, filed 10/31/08, with respect to the rejection of claims 24-31, 35, 38, 40-43 and 45-48 under 35 U.S.C. 102(b) as being anticipated by Price et al. (US 4,128,658) have been fully considered but are not persuasive.

Applicants maintain that the Cutina HR of Price et al. does not fall within the scope of "castor oil" as used in the context of the present invention, because Cutina HR is a hydrogenated castor oil, which is a solid rather than a liquid. Applicants have

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amended independent claims 24, 41, and 46 to specify that the oily substance is selected from the group of neutral oil, sesame oil, peanut oil, olive oil, almond oil, soybean oil, coconut oil, cottonseed oil, corn oil, rape oil, sunflower oil, wheat kernel oil liquid paraffin, wax solutions in organic oil, and low viscosity wax as directly supported by the paragraph bridging pages 9 and 10 of the instant specification. Applicants argue that in so far as Price et al. fail to teach or suggest the oily substances as presently claimed, this reference can not be held to anticipate the subject matter of the instant invention.

This is not persuasive because the claim limitation of an “oily substance” is anticipated by the oily substance Cutina HR, as taught by Price. Even though Cutina HR is a hydrogenated castor oil, it is still an oil or an “oily substance”. The solution of Cutina HR in Example (c) of Price is clearly used to moisten or wet the mixture. This meets the limitation of wetting a mixture of active ingredients and retarding agents. A solution with an oil will, by definition, be “oily”. Therefore, the solution of Cutina HR, as taught by Price, anticipates the “oily substance” limitation of instant claim 24. Price teaches that the moistened mixture in Example (c) is then granulated. This meets the granulation limitation of instant claim 24.

Therefore, the rejection of 07/31/08 is maintained.

Rejection of claims 32-33, 36-37, 39 and 44 under 35 USC § 103(a)

7. Applicants’ arguments, see Page 9, filed 10/31/08, with respect to the rejection of claims 32-33, 36-37, 39 and 44 under 35 U.S.C. 103(a) as being unpatentable over

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Price et al. (US 4,128,658) in view of Santus et al. (US 5,472,704) have been fully considered but are not persuasive.

Applicants argue that Price et al. fail to teach the use of the oily substances set forth in the claims as currently presented. Applicants argue that in so far as Santus et al. fail to compensate for the deficiencies in the teachings of the primary reference, the combined teachings of Price et al. and Santus et al. cannot be held to make the present invention obvious. Applicants argue that the oily substances as presently claimed form an even coating over the particles thereby negating the undesirable properties of the active ingredient particles, e.g., their hydrophilic or corrosive properties and that such a technical advantage cannot be achieved using the Cutina HR in Industrial Methylated Spirit of Price et al. as this substance will precipitate on the surface of the granules upon evaporation of the solvent and lead to an uneven coating (see Declaration of Dr. Otto of record). Applicants argue that the oily substance of the present invention has an entirely different effect than the Cutina HR solution of the cited art such that it would not be obvious to substitute the Cutina HR of Price et al. with the oily substances as presently set forth in claims 24, 41 and 46 and claims dependent therefrom.

This is not persuasive because the fact that Cutina HR will precipitate on the granules shows that there is a barrier formed on the granules. This barrier will intrinsically protect the active ingredient in the particles and will negate the undesirable properties of the active ingredient in the particles, e.g., their hydrophilic or corrosive properties. The Cutina HR taught by Price, being a castor oil, is also a neutral oil.

Therefore, the rejection of 07/31/08 is maintained.

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8. In addition to the maintained rejections, new ground(s) of rejection follow.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 24 recites the Markush group for an oily substance as: "selected from the group consisting of neutral oil, sesame oil, ..." This is an improper Markush group because the broadest reasonable interpretation of "neutral oil" is that it is an oil that does not react or interfere with the composition it is in. The various oils listed in the Markush group (sesame oil, peanut oil ... wheat kernel oil) are considered neutral oils. The term "neutral oil" is a functional limitation. The instant specification, on Page 9, discloses that "neutral oil (Miglyol) is understood to mean a mixture of short- and medium-chained triglycerides, mainly with the fatty acids caprylic acid (C8) and capric acid (C10)". However, instant claim 24 only recites "neutral oil" and the remaining oils can be interpreted to be neutral oils. "While it is appropriate to use the specification to determine what applicant intends a term to mean, a positive limitation from the specification cannot be read into a claim that does not itself impose that limitation."

Please see MPEP 2105.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 24-31, 35, 38, 40-43 and 45-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Price et al. (US 4,128,658).

The claimed invention is a method for preparing granules comprising wetting a mixture of active ingredient(s) and retarding agent(s) with an oily substance and granulating the wetted mixture.

Price teaches a method of producing oral sustained release tablets. “The active ingredient, anhydrous lactose and most of the Cutina HR (a hydrogenated castor oil) are intimately mixed and then the mixture is moistened by mixing with a 10% solution of the remainder of the Cutina HR ... the moistened mass is granulated through a 1.2 mm aperture sieve and dried at 50°C in a fluidised bed dryer. The granules are then passed through a 0.85 mm aperture sieve, blended with the magnesium stearate and compressed ... on a tableting machine with 12.5mm diameter punches” (Col. 29, Example c, lines 29-47). In another exemplified preparation (for an oral syrup), the drug is dissolved in water (Col. 29, line 56). Since the drug dissolves in water it is inherently hydrophilic.

Regarding instant claims 24 and 41, the limitations of a method for preparing granules comprising wetting a mixture of one or more active ingredients and one or

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more retarding agents with an oily substance are anticipated by the granulation method of an active ingredient mixed with anhydrous lactose and a hydrogenated castor oil taught by Price (Col. 29, Example c, lines 29-47). The retarding agent is the lipophilic hydrogenated castor oil. The wetting of the mixture is anticipated by the moistening by the hydrogenated castor oil. The granulation step is anticipated by the fluidized bed granulation step taught by Price. The limitation of compressing the granules so that tablets are prepared of instant claim 41 is anticipated by the compression of granules to form tablets as taught by Price. The limitation of the oily substance is anticipated by the CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47). The broadest reasonable interpretation of “neutral oil” is of an oil that does not interfere or react with the formulation.

Regarding instant claim 25, the limitation of the mixture further comprising excipients is anticipated by the excipient anhydrous lactose taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 26, the limitation of wetting the mixture by spraying is anticipated by the fluidized bed spray dryer taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 27, the limitation of wetting the mixture at room temperature is anticipated by method taught by Price (Col. 29, Example c, lines 29-47). Since Price does not disclose a specific temperature for the wetting or moistening step, one skilled in the art can readily envisage that the process is carried out at room temperature.

Regarding instant claim 28, the limitation of a hydrophilic active ingredient is anticipated by the active ingredient that dissolves in water, as taught by Price (Col. 29, line 56). Since the drug dissolves in water it is inherently hydrophilic.

Regarding instant claims 29-30, the limitation of the active ingredient content is anticipated by the 37.5% (1.5Kg/4Kg) of active ingredient as taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 31, the limitation of the lipophilic retarding agent is anticipated by the hydrogenated castor oil taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 35, the limitations of the percentage of the oily substance are anticipated by the 10% (0.4Kg/4Kg) of CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 38, the limitation of the fluidized bed granulator is anticipated by the fluidized bed dryer taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 40, the limitation of compressing the granules into tablets is anticipated by the tablets formed by compressing granules as taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 42, the limitation of mixing the granules with at least one excipient prior to compressing the granules is anticipated by mixing magnesium stearate with the granules before compressing into tablets as taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 43, the limitation of the excipient is anticipated by the lubricant magnesium stearate taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claims 45-48, the limitations of the granules and the tablet are anticipated by the granules and tablet prepared by the method taught by Price (Col. 29, Example c, lines 29-47). The limitation of the oily substance is anticipated by the CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47).

Therefore, the limitations of claims 24-31, 35, 38, 40-43 and 45-48 are anticipated by the teachings of Price.

14. Claims 24-25, 28-30, 35-36, and 45-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Fuisz (US 5,387,431).

Fuisz teaches a method of preparing a substantially solid saccharide-based matrix comprising subjecting a feedstock comprising a mixture of solid maltodextrin and an oleaginous material to conditions of force and temperature (Col. 25, claim 6). The process can be used to prepare pharmaceutical materials and suitable active ingredients, including vitamins and acetaminophen (water soluble actives) are disclosed (Col. 6, line 53 to Col. 7, line 41). Example 16 discloses the preparation of a pharmaceutical containing sucralfate, xanthan gum, corn oil and maltodextrins, including mixing the materials and processing in order to produce a particulate product (Col. 15, lines 14-20).

Regarding instant claim 24, the limitation of a method for preparing granules comprising wetting a mixture of one or more active ingredients and one or more

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retarding agents with an oily substance is anticipated by the method of preparing a particulate pharmaceutical product by mixing an active ingredient (sucralfate) with a retardant (xanthan gum), corn oil and maltodextrin, as taught by Fuisz (Col. 15, Example 16, lines 14-20). When the materials are mixed, the corn oil will "wet" the dry powders. The granulation step is anticipated by the method comprising subjecting the mixture to conditions of force and temperature, as taught by Fuisz (Col. 25, claim 6).

Regarding instant claim 25, the limitation of the mixture further comprising excipients is anticipated by the maltodextrin taught by Fuisz (Col. 15, Example 16, lines 14-20).

Regarding instant claim 28 and 47, the limitation of a hydrophilic active ingredient is anticipated by the vitamins and acetaminophen taught by Fuisz (Col. 6, line 53 to Col. 7, line 41).

Regarding instant claims 29-30, the limitation of the active ingredient content is anticipated by the 10% of active ingredient (sucralfate) as taught by Fuisz (Col. 15, Example 16, lines 14-20).

Regarding instant claims 35-36, the limitations of the percentage of the oily substance are anticipated by the 5% of corn oil taught by Fuisz (Col. 15, Example 16, lines 14-20).

Regarding instant claims 45-46, the limitations of the granules are anticipated by the particulate pharmaceutical product prepared by mixing an active ingredient (sucralfate) with a retardant (xanthan gum), corn oil and maltodextrin, as taught by Fuisz (Col. 15, Example 16, lines 14-20).

Therefore, the limitations of claims 24-25, 28-30, 35-36, and 45-47 are anticipated by the teachings of Fuisz.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. Claims 32-33, 36-37, 39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (US 4,128,658) in view of Santus et al. (US 5,472,704).

The teaching of Price is stated above.

Price does not expressly teach the combination of the lipophilic retarding agent with a hydrogel matrix forming agent or a structural matrix forming agent.

Santus teaches bioadhesive granules with matrix units for the controlled release of furosemide (Col. 8, lines 63-64, Example 1). A hydrophobic matrix is obtained by granulation with melted excipients (Col. 8, lines 66-67). "50 parts of furosemide are mixed with 25 parts of hydrogenated castor oil and the resulting mixture is kneaded using 25 parts of melted hydrogenated castor oil as a granulation fluid. The resulting mixture is granulated ... the granules are mixed with ... an acrylic copolymer and ... hydroxypropylmethylcellulose ... the mixture is then tableted in an eccentric press ... obtaining tablets with a diameter of 21mm. The tablets are then crumbled and sieved so as to obtain granules ..." (Col. 9, lines 1-12). A fluid bed system (WURBTER-GLATT®)

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is disclosed (Col. 8, lines 58-59). Excipients that are commonly known in the art are disclosed (Col. 7, lines 1-5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of producing granules with an active ingredient and a lipophilic retarding agent, as suggested by Price, combine it with the method of producing granules of active ingredients with a lipophilic retarding agent in combination with acrylic copolymer and hydroxypropylmethylcellulose, as taught by Santus, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Santus teaches that cellulose derivatives such as hydroxypropylmethylcellulose (HPMC) are bioadhesive polymers. One of ordinary skill in the art would know that bioadhesive polymers are crucial for extended release formulations and would include it for extending the release of hydrophilic active ingredients.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claims 32-33, the limitations of the structural matrix forming agent and hydrogel matrix forming agent would have been obvious to one skilled in the art over the HPMC taught by Santus (Col. 9, lines 1-12). The limitation of the water

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soluble excipients would have been obvious over the anhydrous lactose taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 36, the percentage range of the oily substance would have been obvious over the 10% (0.4Kg/4Kg) of CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47). One skilled in the art would modify the level of the oily substance during the process of routine experimentation in order to optimize the sustained or extended release attributes and the stability of the resultant granules.

Regarding instant claim 37, the limitation of the granules further comprising an outer phase of one or more retarding agents would have been obvious over the microunit coating taught by Santus. The method disclosed can coat individual microunits (Col. 8, lines 36-40).

Regarding instant claim 39, the limitation of the granule binder would have been obvious over the HPMC taught by Santus (Col. 9, lines 1-12).

Regarding instant claim 44, the limitation of the tablet further comprising a coating would have been obvious over the tablets taught by Price (Col. 29, Example c, lines 29-47) and because one skilled in the art would employ tablet coatings during the process of routine optimization in order to enhance the stability and shelf-life of the tablet, to mask the off-notes, and to provide a layer of sustained release coating for extending the therapeutic effect of the chosen active ingredient.

Conclusion

13. No claims are allowed.

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14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615